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interferences

FACSIMILE COVER SHEET

DATE: September 5, 2006

TO: BOARD OF PATENT APPEALS AND INTERFERENCES

COMPANY OR FIRM: PTO

FACSIMILE NO.: (571) 273-0052

FROM: Beth Pearson-Naul for Gene L. Tyler

RE: **Serial No.: 09/810,956**
Appeal No.: 2006-0612
Docket No.: COS-822 (APIP-1065)
Title: "Heat-Seal Films and Method of Manufacture"

NUMBER OF PAGES INCLUDING THIS COVER SHEET: 38

IF ANY OF THESE PAGES ARE NOT RECEIVED, PLEASE CALL BETH AT (713) 266-1130, ext. 117

Attached herewith for filing is a Reply Brief for Appellants for the above-referenced patent application.

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this correspondence is being transmitted by facsimile to the attention of the Office of Patent Publications, facsimile no. (571) 273-8300 on this 5th day of September, 2006.

Beth Pearson-Naul

PATENT

BEFORE THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of: Hanyu, et Al.	§ Appeal No. 2006-0612
U.S. Serial No.: 09/810,956	§ Group Art Unit: 1773
Filed: 3/16/2001	§ Examiner: Donald L. Tarazano
For: HEAT-SEAL FILMS AND METHOD OF MANUFACTURE	§ Docket No. COS-822 (APIP-1065)
	§ Date: September 5, 2006

REPLY BRIEF FOR APPELLANTS

Commissioner for Patents
Alexandria, Virginia 22313-1450

Sir:

Appellants hereby submit this, their reply brief, in response to the Examiner's Supplemental Answer which was mailed on July 14, 2006

The final page of this brief bears the attorney's signature.

Comments and Arguments

The comments and arguments that follow are to be read in addition to those already on file with the Board of Appeals and are intended to be considered as a supplement to and not a replacement for those arguments. In the interests of brevity and judicial economy, the earlier arguments are not reproduced, but are relied upon by the Appellants.

You do not have an objection to the Examiner's statement at section 7 that since there was no "grouping of the claims," the claims must all stand or fall together (as you mentioned in your email).

New Ground for Rejection

The Examiner, pursuant to the directions of the Board on remand, obtained a full translation of JP-11-060833. In the supplemental answer, the Examiner states that the basis of the rejection remains the same, but that the rejections have been embellished based upon the results of the full translation.

The embellishment of the rejection amounts to a new ground for rejection because it is based upon a document provided to the Appellants after the close of prosecution. The document is effectively a new document because there are material differences between the original computer translation and the newly presented translated document, hereinafter "Japanese Translation," not the least of these being that the sections of the "reference" detailing the production of exemplary materials is now comprehensible. The examples were incomprehensible in the original computer translation.

The two month time period in which to reply to the Examiner's Supplemental Answer is far shorter than the 6 month period normally granted to an Applicant in which to respond to a new rejection.

Since the Examiner has not characterized the "embellished" rejection as a new rejection, the Appellants are left with little choice but to continue the Appeal. MPEP 1208 sets forth that:

> In response to the following, however, appellant is required to file either a reply brief to maintain the appeal or a reply under 37 CFR 1.111 to reopen prosecution:
> (A) An examiner's answer that contains a new ground of rejection pursuant to 37 CFR

> 41.39 (see MPEP § 1207.03); or
> (B) A supplemental examiner's answer responding to a remand by the Board for further consideration of a rejection pursuant to 37 CFR 41.50(a) (see MPEP § 1207.05). Such a supplemental examiner's answer may contain a new ground of rejection (also see MPEP § 1207.03).

Since 37 CFR 1.111 is limited to a reply by applicant or appellant to a non-final rejection, the Appellants have no choice but to file a reply brief and continue the appeal in the present case.

The Appellants believe that the claims under appeal are patentable, even in view of the Japanese Translation. However, in the event that the Board may disagree, the Appellants request that the Board of Appeals remand the present case to the Examiner to reopen prosecution rather than upholding the rejections. Any other action would unfairly prejudice the Appellants in view of their entitlement to respond to the evidence upon which the Board relies to maintain a rejection. (*See*, IN RE SUJEET KUMAR, HARIKLIA DRIS REITZ, XIANGXIN BI, and NOBUYUKI KAMBE, 418 F.3d 1361, generally and at 1369.)

The Examiner's Statements Regarding the Two Degree Range Difference

At page 8, section 8c of the Examiner's supplemental answer, the Examiner states that a two degree difference in seal initiation temperature should not be considered to be significant and that it "would be scientifically irresponsible to believe that the applicants value of 125°C is clearly different from a value of 127°C as is reported." Presumably, it is on the basis of his own knowledge that the Examiner is stating the seal initiation temperature test is too subject to error to be trusted to report results having a resolution of one degree centigrade.

If the Examiner is correct and the seal initiation temperature test lacks sufficient resolution to report seal initiation temperatures with a resolution of one degree centigrade, then "responsible" scientists and inventors would report seal initiation temperatures with an appropriate round off, such as a round off to 5 or 10 degrees centigrade. Surprisingly, the Examiner denies the significance of a two degree difference in seal initiation temperature and states that it is irresponsible to report such results, yet

the examiner cites the Japanese Translation as his primary reference and this reference is one that reports seal initiation temperature differences with a resolution of 1 degree in Table 1. The inventors of the Japanese Translation reference are not alone in making such reports. The Appellants' assignee is at least consistent in that they report a seal initiation temperature of 94°C in U.S. Patent No. 6,641,913 at col. 11, line 62. Exxon Chemical reports seal initiation temperature values of 111, 101, and 97 °C in table II at column 15 of U.S. Patent Number 5,530,065. Clearly, not everyone shares the Examiner's opinion that a one degree difference or resolution in seal initiation temperature, much less a two degree difference in seal initiation temperature, is insignificant. The Appellants assert that the two degree difference is significant and sufficient to rebut the Examiner's anticipation rejection and the Board is requested to overturn this ground of rejection.

The Examiner's Statements Regarding the Obviousness Rejections

The Appellants offer the following citation which is more recent than that filed with the Appellants' Appeal Brief:

> "If all the elements of an invention are found in a combination of prior art references, 'a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.' (Velander v. Garner, 348 F.3d 1359, 63 (Fed. Cir. 2003). (*Citing*, In re Vaeck, 947 F.2d 488, 493 (Fed. Cir. 1991) (*citing*, In re Dow Chem. Co., 837 F.2d 469, 473 (Fed. Cir. 1988)).)

The Japanese Translation, at page 4, paragraph 0003, states that the problem to be solved by the invention disclosed therein is to provide a polypropylene that can be used to prepare excellent films having a balanced low-temperature heat sealability, rigidity, impact resistance, and antiblocking properties. One of ordinary skill in the art of preparing films from polymers would not have been motivated by this reference to produce a film having substantially lower heat seal initiation temperatures than those reported in the application, since it would be intuitive that they had achieved the lowest seal initiation temperatures possible to meet their stated goals. While a reference does not have to be enabling, it should at least be sufficiently descriptive to give one of ordinary skill a reasonable expectation of success. The Japanese Reference, even as

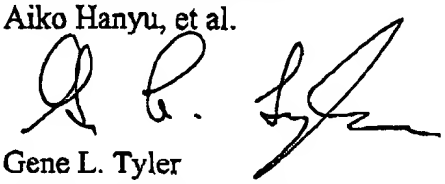
translated, does not rise to that level because it implicitly teaches that they have gone as low as you can go with that technology The Appellants respectfully request the Board to reverse the Examiner's obviousness rejections.

PRAYER FOR RELIEF

It is respectfully submitted that the rejections of the claims have been overcome and/or avoided by the arguments presented above. It is further respectfully requested that the Board reverse the final rejections of the Examiner

No fee is believed due for the filing of this paper. The Commissioner is authorized to charge any additional fees or credit any overpayments to Deposit Account **13-0010 (APIP-1065US).**

Respectfully submitted,
Aiko Hanyu, et al.



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LEXSEE 418 F.3D 1361

IN RE SUJEET KUMAR, HARIKLIA DRIS REITZ, XIANGXIN BI, and NOBUYUKI KAMBE

04-1074

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

418 F.3d 1361; 2005 U.S. App. LEXIS 17215; 76 U.S.P.Q.2D (BNA) 1048

August 15, 2005, Decided

PRIOR HISTORY: [**1] Appealed from: United States Patent and Trademark Office Board of Patent Appeals and Interferences. (Serial No. 09/136,483).

DISPOSITION: VACATED AND REMANDED.

COUNSEL: Peter S. Dardi, Patterson, Thuente, Skaar & Christensen, P.A., of Minneapolis, Minnesota, for appellants. With him on the brief was Tye Biasco. Of counsel were Randall T. Skaar and Eric H. Chadwick.

John M. Whealan, Solicitor, Office of the Solicitor, of Arlington, Virginia, for the Commissioner of Patent and Trademarks. With him on the brief were James R. Hughes and Stephen Walsh, Associate Solicitors.

JUDGES: Before NEWMAN, Circuit Judge, ARCHER, Senior Circuit Judge, and DYK, Circuit Judge. NEWMAN, Circuit Judge.

OPINION:

[*1363] Sujeet Kumar, Hariklia Dris Reitz, Xiangxin Bi and Nobuyuki Kambe (together "Kumar") appeal the decision of the Board of Patent Appeals and Interferences of the Patent and Trademark Office, rejecting claims 1-3, 5-16, and 19-22 of patent application Serial No. 09/136,483 entitled "Aluminum Oxide Particles" as obvious under *35 U.S.C. § 103*. We vacate the Board's decision and remand for further proceedings.

BACKGROUND

The claims of Kumar's patent application are directed to aluminum oxide [**2] particles of submicron (nanometer) size, n1 having a specified size range and size distribution. The specification describes the production of the particles by laser pyrolysis, but the claims at issue are directed to the particles themselves, independent of their method of production. Due to their very small size and high degree of uniformity, the particles are described as well suited for use in polishing compositions.

n1 One micron equals 1,000 nanometers (nm).

The examiner had rejected all of the product claims, and on appeal the Board treated claims 1 and 19 as representative. Process claims have been allowed, and are not at issue. Kumar agrees that all of the claims on appeal rise or fall with claims 1 and 19.

1. A collection of particles comprising aluminum oxide, the collection of particles having

an average diameter of primary particles from about 5 nm to about 500 nm and

less than about one in 10 6 particles have a diameter greater than about three times the average diameter of the collection of particles.

[*1364] 19. A collection of particles comprising aluminum oxide, the collection of particles having

an average diameter from about 5 nm to about [**3] 500 nm and

a distribution of particle sizes such that at least about 95 percent of the particles have a diameter greater than about 40 percent of the average diameter and less than about 160 percent of the average diameter.

The Board held the claims unpatentable on the ground of obviousness in view of *U.S. Patent No. 5,389,194* (the Rostoker patent), which shows aluminum oxide particles of nanometer size. The Board found that the particle sizes and size distributions n2 of the Rostoker particles and of Kumar's claimed particles are overlapping. Kumar concedes that the Rostoker particles overlap the Kumar particles in average particle size, but argues that they do not overlap in particle size distribution. The appeal relates primarily to the Board's procedure, wherein the values deemed to overlap appear for the first time in the Board's decision. Kumar states that he was unfairly precluded from replying to this evidence, and that the Board improperly refused to consider the responsive evidence submitted with Kumar's request for reconsideration.

n2 The parties explain the difference between average particle size and particle size distribution with an analogy using balls: a collection of (1) softballs, baseballs and tennis balls may have the same average size as a collection of (2) basketballs, baseballs and golf balls, but group (2) has a larger size distribution.

[**4]

The Board's calculations were derived from the Rostoker reference, which describes aluminum oxide having a particle size and size distribution as follows:

According to the invention, the alpha aluminum oxide particles used for polishing exhibit the following characteristics. Preferably, the particle size is "X" nm, and the distribution of particle sizes is controlled to within "Y" nm, and the particles used for polishing are "Z" percent (%) in the alpha phase, where:

"X" is 10-100 nm, such as 10, 20, 30, 40 or 50 nm, and is preferably no greater than 50 nm; and

"Y" is approximately "P" percent of "X", where "P" is 10%, 20%, 30%, 40% or 50%, and is preferably no greater than 50% to ensure a narrow (Gaussian) distribution of particle sizes about "X";

"Z" is at least 50%, including at least 60%, 70%, 80% and 90%, and as high as 100%.

A quality factor "Q" is inversely related to "Y", and is a measure of the distribution of particle sizes. "Q" can be calculated as the concentration of particles at the desired size "X", divided by the range of sizes of particles at 3 db (decibels) lower than "X". Preferably, the size distribution of alpha aluminum oxide particles used for polishing [**5] exhibits a "Q" of at least 10, including 10, 50, 100, 500, 1000, 5000, or 10,000 Q" ("is dimensionless).

Rostoker patent, col. 7, lines 4-27. The Board selected "X" and "P" values in the range disclosed by Rostoker, 10 nm and 10% respectively, to calculate a "Y" value of 1 nm (10 nm times 10% equals 1 nm), within which Rostoker's size distribution is controlled; this results in a particle size distribution range of 9-11 nm (10 nm +/- 1). The Board found that this distribution range overlaps with the range in Kumar's claim 1, which the Board calculated to be 0-30 nm based on a particle size distribution controlled to within three times the average diameter (10 nm times 3 equals 30 nm). Thus the Board found that the Rostoker and Kumar distributions overlap.

[*1365] Similarly, the Board selected "X" and "P" values in the range described by Rostoker, to calculate a "Y" value of 5 nm (10 nm times 50% equals 5 nm); this results in a Rostoker distribution range of 5-15 nm (10 nm +/- 5). The Board found that this range overlaps with the range in Kumar's claim 19, which the Board calculated to be 4-16 nm based on the Kumar particle size distribution controlled to within 40-160% of the average [**6] diameter (10 nm times 40% and 160% equals 4 and 16 nm, respectively). The Board held that these overlapping values, and others shown by its calculations, established a *prima facie* case of obviousness of the Kumar particles.

These calculations had not been made by the examiner, and according to the record were not presented during the argument of the appeal to the Board. The Board apparently made these calculations during its decision of the appeal. The Board included these calculations in an Appendix to its decision, holding that they support a *prima facie* case of obviousness and that Kumar's evidence had not rebutted the *prima facie* case. Kumar's evidence included a declaration by co-inventor Dr. Kambe to the effect that Rostoker does not enable one of ordinary skill in the field of the invention to produce particles having Kumar's size range and distribution. Kumar cited *Beckman Instruments, Inc. v. LKB Produkter AB, 892 F.2d 1547, 1551 (Fed. Cir. 1989)*, for the rule that "in order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method." See also *Motorola, Inc. v. Interdigital Tech. Corp., 121 F.3d 1461, 1471 (Fed. Cir. 1997)*; [**7] *In re Payne, 606 F.2d 303, 314 (CCPA 1979)*. The Board rejected the Kambe declaration, finding that Mr. Kambe's assertions were conclusory and unsupported by evidence.

Kumar requested Board reconsideration, submitting the declaration of Dr. Rajiv Singh, Professor of Materials Science and Engineering at the University of Florida at Gainesville. Professor Singh explained that Rostoker's "Q" value defines size distribution, and criticized Rostoker's description of the "Q" value as internally inconsistent and not in conformity with standard representations of distribution functions. Professor Singh pointed out that Rostoker stated that he used the manufacturing method of Siegel, *U.S. Patent No. 5,128,081*, and opined that Siegel does not produce submicron particles. The Board refused to consider Professor Singh's declaration, ruling that Kumar had not shown good and sufficient reason why it was not earlier presented.

Kumar appeals, stating that a *prima facie* case of obviousness was not established, or if established was rebutted. Kumar objects to the tardy submission of the Board's calculations and states that he was entitled to consideration of Professor Singh's evidence. [**8] Kumar argues that the Singh evidence rebuts the *prima facie* case and that the Board should have either considered it or remanded to the examiner for that purpose.

DISCUSSION

Determination of obviousness under *35 U.S.C. § 103* is a legal conclusion based on underlying facts. *Graham v. John Deere Co., 383 U.S. 1, 17, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966)*; *In re Oetiker, 977 F.2d 1443, 1444 (Fed. Cir. 1992)*; *In re Piasecki, 745 F.2d 1468, 1471 (Fed. Cir. 1984)*. We give plenary review to the Board's legal conclusion, whereas the underlying factual determinations are reviewed to ascertain whether they are supported by substantial evidence. *In re Gartside, 203 F.3d 1305, 1316 (Fed. Cir. 2000)*. Substantial evidence is "such relevant

[*1366] evidence as a reasonable mind might accept as adequate to support a conclusion." *Consolidated Edison Co. v. NLRB, 305 U.S. 197, 229, 83 L. Ed. 126, 59 S. Ct. 206 (1938).*

During examination, the examiner bears the initial burden of establishing a *prima facie* case of obviousness. *Oetiker, 977 F.2d at 1445.* The *prima facie* case is a procedural tool, and requires [**9] that the examiner initially produce evidence sufficient to support a ruling of obviousness; thereafter the burden shifts to the applicant to come forward with evidence or argument in rebuttal. *Piasecki, 745 F.2d at 1475.* When rebuttal evidence is provided, the *prima facie* case dissolves, and the decision is made on the entirety of the evidence. *Oetiker, 977 F.2d at 1445; In re Spada, 911 F.2d 705, 708 (Fed. Cir. 1990); In re Rinehart, 531 F.2d 1048, 1052 (CCPA 1976).*

A

A *prima facie* case of obviousness may be made when the only difference from the prior art is a difference in the range or value of a particular variable. *In re Peterson, 315 F.3d 1325, 1329 (Fed. Cir. 2003); In re Woodruff, 919 F.2d 1575, 1578 (Fed. Cir. 1990).* The Board found that Rostoker suggests restricting the particle size distribution to a range of 9-11 nm, which overlaps Kumar's claim 1 limitation of 0-30 nm when an average diameter of 10 nm is selected for the Rostoker particles (10 nm times 3 equals 30 nm). The Board similarly found that Rostoker suggests restricting particle size distribution [**10] to a range of 5-15 nm, which overlaps Kumar's claim 19 distribution of 4-16 nm when an average diameter of 10 nm is selected (10 nm times 40% and 160% equals 4 and 16 nm, respectively).

Kumar argues that Rostoker's description of its particles is too indefinite to support any particular distribution of particle sizes. Kumar states that a skilled artisan would not understand Rostoker's "Y" variable to have the values that the Board calculated because Rostoker, in addition to stating that "Y" is approximately "P" percent of "X," requires that its particles meet a quality factor "Q "that is inversely related to "Y." Kumar argues that this renders the calculation of "Y" more complex than the Board's simplified calculation, and that Rostoker does not disclose the values the Board calculated and then used to conclude that Kumar's size distribution overlaps with that of Rostoker. Kumar also states that the Board should have provided an opportunity to support this argument with evidence showing that the Rostoker teachings do not support the Board's *sua sponte* calculations. Kumar states that the Singh declaration establishes the indefiniteness of the Rostoker reference, and challenges [**11] the assumptions underlying the Board's calculations.

The PTO responds that Rostoker's quality factor "Q" describes the extent to which his particle size distribution is controlled to within certain limits of the target particle size. The PTO suggests that Q is calculated as follows: Rostoker calls for the division of the amount of particles at the desired size X, by the amount of particles at a size 3 decibels ("db") from X. To find a value 3 db from X, which the Board labels "A," one must solve the logarithmic function, 10 log (X/A) = 3 db. The PTO solves this function and finds that if log (X/A) = 3/10, then X/A = 10 3/10, and thus X/A = 2, and A = X/2. This means that a value that is 3 db lower than X is 2 X/or 50% of X. Thus the PTO states that the quality factor Q merely describes the extent to which the particles are within 50% and 150% of the target particle size. For example, the "Q" value of 10,000 in the Rostoker reference indicates a high quality

[*1367] product in which 10,000 particles are of the target size for every particle at 50% or 150% of the target size. According to the PTO, rather than making indefinite the values for "X" and "Y" as shown by Rostoker and the ranges of [**12] those values, the "Q" factor provides an independent description of Rostoker's particle size distribution.

The PTO also responds that the Board was correct in refusing to consider the Singh declaration because its execution date shows that it was prepared before the Board issued its initial decision, and thus could have been earlier presented. Kumar states that the Singh declaration was prepared for use in a different patent application, and that its relevance to this application became manifest only after the Board's decision.

The values identified by the Board's calculations were not contained in the prior art or any examination record, but appeared for the first time in the Board's opinion. Although the PTO argues that the calculations the Board included in its decision were not new evidence, but simply an additional explanation of the Board's decision, these values produced and relied on by the Board had not previously been identified by the examiner or the Board. Kumar was entitled to respond to these calculations, and the Board committed procedural error in refusing to consider the evidence proffered in response. See *In re De Blauwe, 736 F.2d 699, 706 n. 9 (Fed. Cir. 1984)* [**13] ("Where the board makes a decision advancing a position or rationale new to the proceedings, an applicant must be afforded an opportunity to respond to that position or rationale by submission of contradicting evidence"). The PTO regulations so require. See 37 C.F.R. § 1.196(b) ("when the Board . . . makes a new rejection of an appealed claim, the appellant may . . . submit . . . a showing of fact . . . and have the matter reconsidered").

Instead of basing its decision on the values directly disclosed by Rostoker, the Board "went off on its own in considering the differences" between Rostoker and the Kumar invention, see *In re Eynde, 480 F.2d 1364, 1371 (CCPA 1973)*, the Board calculating particular distribution values based on the assumption that the Rostoker variables "X," "Y," "P," and "Q" would be understood by a skilled artisan in the same way in which they were understood by the Board. The Singh declaration challenges the Board's view of the Rostoker variables. While the PTO now argues that there is no merit to the Singh position, and offers its own explanation for the meaning of the "Q" variable, the merits of this evidence are not properly debated in [**14] the first instance on appeal. There is no record on this aspect, for the Board refused to consider it.

In accordance with the *Administrative Procedure Act*, the agency must assure that an applicant's petition is fully and fairly treated at the administrative level, without interim need for judicial intervention. See *Dickinson v. Zurko, 527 U.S. 150, 154, 144 L. Ed. 2d 143, 119 S. Ct. 1816 (1999)* (the PTO is an agency subject to the Administrative Procedure Act). The Board's rules are in accord. See 37 C.F.R. § 1.196(b) (when the Board relies on a new ground of rejection, it is appropriate to provide the applicant with an opportunity to respond to that ground).

When a rejection for obviousness is based on overlapping values in the prior art, identification of the values deemed to overlap is material to the rejection. In this case the overlapping values were identified for the first time in the decision of the Board, and are not themselves set forth in Rostoker or any other reference.

[*1368] In calculating the overlapping values, the Board found facts not found by the examiner regarding the differences between the prior art and the claimed invention, which in fairness required an opportunity [**15] for response. See *In re Kronig, 539 F.2d 1300, 1302 (CCPA 1976)* ("the ultimate criterion of whether a rejection is considered 'new' in a decision by the board is whether appellants have had fair opportunity to react to the thrust of the rejection").

We conclude that the Board's calculations and its decision based thereon constituted a new ground of rejection, and should have been so treated. See *In re Waymouth, 486 F.2d 1058, 1060-61 (CCPA 1973)* (holding that a new rejection had occurred where the examiner and the board rejected a claim for different reasons).

B

Kumar also argues that even if a *prima facie* case of obviousness were established, Kumar rebutted that case with evidence and argument that Rostoker did not enable the Kumar product, and that the Board erred in refusing to consider the rebuttal evidence.

An applicant may rebut a *prima facie* case of obviousness by providing a "showing of facts supporting the opposite conclusion." Such a showing dissipates the *prima facie* holding and requires the examiner to "consider all of the evidence anew." *Piasecki, 745 F.2d at 1472*; *In re Rinehart, 531 F.2d 1048, 1052 (CCPA 1976)*. [**16] Rebuttal evidence may show, for example, that the claimed invention achieved unexpected results relative to the prior art, *In re Geisler, 116 F.3d 1465, 1469-70 (Fed. Cir. 1997)*; that the prior art teaches away from the claimed invention, *id. at 1471*; that objective evidence (e.g., commercial success) supports the conclusion that the invention would not have been obvious to a skilled artisan, *Piasecki, 745 F.2d at 1475*; or that the prior art did not enable one skilled in the art to produce the now-claimed invention, *In re Payne, 606 F.2d 303, 314-15 (CCPA 1979)*.

Although published subject matter is "prior art" for all that it discloses, in order to render an invention unpatentable for obviousness, the prior art must enable a person of ordinary skill to make and use the invention. *Beckman Instruments, 892 F.2d at 1551*. Thus when a *prima facie* case of obviousness is deemed made based on similarity to a known composition or device, rebuttal may take the form of evidence that the prior art does not enable the claimed subject matter. See *Payne, 606 F.2d at 314-15* (" the presumption [**17] of obviousness based on close structural similarity is overcome where the prior art does not disclose or render obvious a method for making the claimed compound"); *In re Hoeksema, 55 C.C.P.A. 1493, 399 F.2d 269, 274 (CCPA 1968)* ("the absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious, based on close relationships between their structures and those of prior art compounds").

The applicant has the burden of coming forward with evidence in rebuttal, when the prior art includes a method that appears, on its face, to be capable of producing the claimed composition. This burden may be met by presenting sufficient reason or authority or evidence, on the facts of the case, to show that the prior art method would not produce or would not be expected to produce the claimed subject matter. Since Rostoker states that its particles were made by the method shown in the Siegel patent, it was reasonable for Kumar to argue that the Siegel process would not produce Kumar's particles. Kumar's

[*1369] argument was supported by the declarations of Drs. Kambe and Singh. Whether these expert declarations are sufficient, without [**18] experimental data or other evidence, is a question of fact to be determined on the record. Although the PTO now argues that the Singh declaration is insufficient, the Board erred in refusing to consider the Singh declaration, for Kumar correctly observed that the issue was not presented until the Board made its *sua sponte* calculations of particle size distribution. The Board's calculations raised new issues regarding enablement because they suggest particle size distributions Rostoker should be enabled to attain. In addition, although the Board found the Kambe declaration conclusory and insufficient to rebut the *prima facie* case of obviousness, this declaration must be re-evaluated in light of the Singh declaration. See *Rinehart, 531 F.2d at 1052* (when evidence is submitted to rebut a *prima facie* case of obviousness, the decision maker must consider all of the evidence anew).

The PTO argues that as long as Rostoker enables the Rostoker invention, Rostoker renders the Kumar invention obvious, even if Kumar shows that Rostoker does not enable the Kumar invention. That is incorrect. To render a later invention unpatentable for obviousness, the prior art must [**19] enable a person of ordinary skill in the field to make and use the later invention. *Beckman Instruments, Inc., 892 F.2d at 1551*; *Payne, 606 F.2d at 314*. Thus the relevant inquiry is not whether the Rostoker patent was invalid for lack of enablement, but whether Rostoker enabled persons skilled in this art to produce particles of the size and distribution claimed by Kumar. Of course, if it were shown that the Rostoker product could not be produced by the Rostoker method, that would be relevant evidence concerning whether Rostoker rendered obvious the Kumar product. Kumar points out that his method of laser pyrolysis is quite different from that used by Rostoker.

After the Board adduced its calculations of particle size and distribution, Kumar was entitled to offer evidence in rebuttal, for consideration by the Board or on return to an examiner. The entirety of the evidence must be reviewed in order to determine whether the claimed invention as a whole would have been obvious to a person of ordinary skill in the field. See *Rinehart, 531 F.2d at 1052*.

CONCLUSION

In view of our holding that Kumar was entitled to respond to the evidence [**20] adduced *sua sponte* by the Board, we vacate the Board's decision and remand for appropriate further proceedings.

VACATED AND REMANDED

LEXSEE 348 F.3D 1359

WILLIAM H. VELANDER, WILLIAM N. DROHAN, HENRYK LUBON (DECEASED) and JOHN L. JOHNSON (DECEASED), Appellants, v. IAN GARNER, MICHAEL L. DALRYMPLE, DONNA E. PRUNKARD, and DONALD C. FOSTER, Appellees.

02-1366 Interference No. 104,242

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

348 F.3d 1359; 2003 U.S. App. LEXIS 22717; 68 U.S.P.Q.2D (BNA) 1769

November 5, 2003, Decided

SUBSEQUENT HISTORY: Counsel Corrected November 5, 2003.

PRIOR HISTORY: [**1] Appealed from: United States Patent and Trademark Office, Board of Patent Appeals and Interferences.

DISPOSITION: Affirmed.

COUNSEL: R. Elizabeth Brenner, Foley & Lardner, of Washington, DC, argued for appellants. With her on the brief were Stephen A. Bent and Jack L. Lahr.

James F. Haley, Jr., Fish & Neave, of New York, New York, argued for appellees. With him on the brief was Karen Mangasarian.

JUDGES: Before SCHALL, GAJARSA, and PROST, Circuit Judges. Opinion for the court filed by Circuit Judge SCHALL, in which Circuit Judge PROST joins. Dissenting opinion filed by Circuit Judge GAJARSA.

OPINIONBY: SCHALL

OPINION: [*1361] SCHALL, Circuit Judge.

This appeal stems from an interference proceeding involving the claims of United States Patent Application Serial No. 08/443,184 (the "'184 application") and *United States Patent No. 5,639,940* (the "*'940 patent*"). William H. Velander, William N. Drohan, Henryk Lubon (deceased), and John L. Johnson (deceased) (collectively "Velander") are the inventors named on the '184 application. Ian Garner, Donna E. Prunkard, and Donald C. Foster (collectively "Garner") are the inventors named on the *'940 patent*. Velander appeals the decision of the United States Patent and Trademark [**2] Office, Board of Patent Appeals and Interferences ("Board"), that granted Garner's preliminary motion to have all of the allowed claims of the '184 application held unpatentable as obvious over the prior art. *Garner v. Velander, 2001 Pat. App. LEXIS 65, Interference No. 104,242 (B.P.A.I. Aug. 16, 2001)* ("Velander"). Because the decision of the Board is supported by substantial evidence and is not contrary to law, we affirm.

BACKGROUND

I.

This case relates to the production of non-human mammals that have been genetically altered ("transgenic animals") so that they produce the enzyme fibrinogen in its biologically active state. After the enzyme is produced, it is recovered from the milk of the mammal. The fibrinogen enzyme consists of two copies of three separate peptides: the Aa chain, the B chain, and the chain.

Fibrinogen is normally synthesized by the liver and plays a key role in blood clotting. An absence of fibrinogen in a human can lead to a malfunction in the blood clotting process. The production and isolation of biologically active fibrinogen can provide a source of fibrinogen to treat individuals suffering from a deficiency of the enzyme. The present interference involves competing claims [**3] to a transgenic animal (and methods to make such an animal) that produces fibrinogen and secretes it into its milk.

II.

The '184 application (also referred to as the "Velander application") was filed on May 17, 1995. The application was afforded the benefit of the February 18, 1994 filing date of its parent application, United States Patent Application Serial No. 08/198,068. The claims of the Velander application are directed to (i) the production of a transgenic animal that expresses a foreign (or

heterologous) biocompetent fibrinogen protein and (ii) a method of producing biocompetent fibrinogen using such an animal.

On March 3, 1994, Garner filed United States Patent Application Serial No. 08/206,176. The *'940 patent* (also referred to as the "Garner patent") issued from that application. Upon issuance, the *'940 patent* was assigned to Pharmaceutical Proteins Ltd. and ZymoGenetics, Inc. The claims of the Garner patent, like those of the Velander application, are directed to both the production of a transgenic animal that expresses a foreign (or heterologous)

[*1362] biocompetent fibrinogen protein and a method of producing biocompetent fibrinogen using such an animal. n1

n1 As used in the *'940 patent*, the term "heterologous" denotes "genetic material originating from a different species than that into which it has been introduced, or a protein produced from such genetic material." *'940 patent*, col. 4, ll. 1-4. As also used in the *'940 patent*, the term "biocompetent fibrinogen" denotes "fibrinogen that polymerizes when treated with thrombin to form insoluble fibrin," in other words, fibrinogen that can perform its biological function. Id. at col. 3, ll. 52-54.

[**4]

On June 30, 1998, the Examiner allowed claims 64-73 of the Velander application, but declared an interference between those claims and the issued Garner patent. The interference was declared on the ground that claims 64-73 of the '184 application and claims 1-33 of the *'940 patent* either corresponded to the proposed interference counts or would require performance of the method in the counts in order to produce the claimed transgenic animals. The interference counts, which corresponded to all of Velander's allowed claims (64-73) and all of Garner's patented claims (1-33), were as follows:

A method for producing biocompetent fibrinogen comprising:

providing a transgenic female non-human mammal carrying in its germline heterologous DNA segments Aa, B, and chains of fibrinogen, wherein said segments are expressed in a mammary gland of said mammal and biocompetent fibrinogen encoded by said segments is secreted into milk of said mammal; collecting milk from said mammal; and recovering said biocompetent fibrinogen from said milk.

OR

A transgenic non-human female mammal that produces recoverable amounts of biocompetent human fibrinogen in its milk, wherein said mammal [**5] comprises:

a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aa chain,

a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen B

chain, and a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen chain, and

further wherein each chain is derived from the same species and is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal.

OR

A non-human mammal carrying in its germline DNA segments encoding Aa, B, and chains of fibrinogen, wherein female progeny of said mammal express said DNA segments in a mammary gland to produce biocompetent fibrinogen.

In due course, after the interference was declared, Garner moved to have Velander's claims 64-73 held unpatentable under *35 U.S.C. § § 102(b) and 103 (2000)*. n2 In its motion, Garner conceded that if it succeeded in having the claims of the Velander application held unpatentable, the claims of the *'940 patent*, all of which included the use of cDNA for the production of fibrinogen, would also be unpatentable. [**6] Garner did, however, maintain that the use of genomic DNA for the production of fibrinogen, as described in Garner's Reissue Application No. 09/232,488, filed January 15, 1999, was still patentable. n3 Because

[*1363] Garner did not identify a single reference that anticipated all of the limitations of any of the claims at issue, the Board stated that it understood Garner's argument to be that the subject matter of Velander's claims was unpatentable under *section 103* in view of *section 102(b)* prior art. Since Velander did not argue that its claims were separately patentable and did not dispute Garner's assertion that either claim 64 or 65 of the '184 application would be a representative claim upon which an obviousness analysis could be based, the Board determined patentability on the basis of claim 65. Claim 65 of the Velander application is as follows:

> n2 Statutory references are to the 2000 version of the United States Code.
>
> n3 In its reissue application, Garner limits the type of DNA that can be used in its claimed method to produce transgenic animals to genomic DNA, excluding cDNA (as in the Velander application). cDNA stands for complementary DNA, or DNA that is synthesized from a messenger RNA template. Genomic DNA is the full complement of DNA contained in the genome of a cell or organism.

[**7]

A transgenic non-human female mammal that produces recoverable amounts of biologically active human fibrinogen that is converted to fibrin upon reaction with human thrombin in its milk, wherein said mammal comprises:

> a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aa chain,
>
> a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen B chain, and
>
> a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen chain, and further wherein each chain is derived from the same species and is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal.

*Velander, 2001 Pat. App. LEXIS 65 at *6.*

III.

Pursuant to *35 U.S.C. § 103(a)*,

> [a] patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

The ultimate determination [**8] of whether an invention would have been obvious under *section 103(a)* is a legal conclusion based on underlying findings of fact. *In re Kotzab, 217 F.3d 1365, 1369 (Fed. Cir. 2000)*. The underlying factual inquiries include (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; and (3) the differences between the claimed invention and the prior art. *Graham v. John Deere Co., 383 U.S. 1, 17, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966)*. If all the elements of an invention are found in a combination of prior art references,

> a proper analysis under *§ 103* requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

In re Vaeck, 947 F.2d 488, 493 (Fed. Cir. 1991) (citing *In re Dow Chem. Co., 837 F.2d 469, 473 (Fed. Cir. 1988)*). Both the suggestion [**9] and the reasonable expectation of success "must be founded in the prior art, not in the applicant's disclosure." *Id.* Before the Board, as the moving party, Garner had the burden of establishing by a preponderance of the evidence that the invention of claim 65 of the Velander application would have been

obvious as of February 18, 1993, one year before the filing of Velander's 08/198,068 application (the "critical date"). *Bruning v. Hirose, 161 F.3d 681, 685-86 (Fed. Cir. 1998)* (holding that co-pending applications, as in an interference proceeding, invoke the preponderance of the evidence standard for validity challenges); *Velander, 2001 Pat. App. LEXIS 65 at *4, 6.*

[*1364] In support of its motion, Garner argued to the Board that all the elements of the '184 application were in the prior art, and that the prior art would have suggested to one of ordinary skill in the art (i) the production of a transgenic animal that would express biocompetent fibrinogen, and (ii) a method of producing biocompetent fibrinogen using such an animal. Garner also argued that the prior art would have revealed that one of ordinary skill would have had a reasonable expectation of success in the production [**10] of such a transgenic animal and in producing biocompetent fibrinogen using that animal. Therefore, Garner contended, Velander's application would have been obvious to one of ordinary skill in the art as of the critical date of February 18, 1993.

In advancing its obviousness argument, Garner contended that the motivation to combine the elements of the invention, which Garner asserted were in the prior art, could be found in a publication by Dr. Lothar Hennighausen n4 (the "Hennighausen Review") and in *United States Patent No. 4,873,316* (the "Meade patent"). Garner pointed out that the Meade patent disclosed a method for the production of heterologous proteins in the milk of transgenic animals, see Meade patent, col. 1, l. 52-col. 4, l. 60, while the Hennighausen Review suggested the production of commercial quantities of plasma proteins in transgenic animals, see Hennighausen Review at 3-4. Citing the Hennighausen Review and the Meade patent, as well as *United States Patent No. 5,304,489* (the "Rosen patent") and Patent Cooperation Treaty application WO 92/00239 of Anthony J. Clark (the "Clark application"), Garner argued that fibrinogen was an obvious target for expression in transgenic [**11] animals. This was so, Garner urged, because the low level expression of fibrinogen demonstrated in cell culture systems was exactly the type of problem that expression in the milk of transgenic animals was designed to overcome. Garner also argued that one of ordinary skill in the art would have had a reasonable expectation of success in producing biocompetent fibrinogen in the milk of transgenic animals in view of the prior art showing successful production of transgenic animals capable of expressing heterologous proteins in biologically active form. As support for that proposition, Garner cited several authorities. n5 Garner contended that since all the elements of the invention described in the '184 application were in the prior art and since the prior art suggested overcoming the problems associated with fibrinogen production, "Velander's results were neither unexpected nor surprising."

n4 Hennighausen, et al., The Mammary Gland as a Bioreactor: Production of Foreign Proteins in Milk, 1 Protein Expression & Purification 3 (1990).

n5 Greenberg et al., Expression of Biologically Active Heterodimeric Bovine Follicle-stimulating Hormone in Milk of Transgenic Mice, 88 P.N.A.S. 8327 (1991); Storb et al., Transgenic Mice with and e Genes Encoding Antiphosphorylcholine Antibodies, 164 J. Experimental Medicine 627 (1986); Burdon et al., Expression of Whey Acidic Protein Transgene During Mammary Development, 266 J. Biol. Chem. 6909 (1991); and Behringer et al., Synthesis of Functional Human Hemoglobin in Transgenic Mice, 245 Science 971 (1989).

[**12]

Velander did not dispute that the elements of claim 65 of the '184 application were in the prior art. Neither did Velander dispute that the prior art contained a motivation to combine those elements. Rather, it argued that there are many variables that affect protein expression levels and that, as of February 18, 1993, the critical date, one of ordinary skill in the art would not have had a reasonable expectation of success in practicing the invention claimed in the '184 application. Velander contended that expression in cell

[*1365] cultures is not predictive of expression levels in transgenic animals and that, generally, expression levels of fibrinogen in transgenic expression systems is extremely variable. Velander Paper No. 41, pp. 15-21. Velander urged that, as of the critical date, a skilled artisan would have had a low expectation of success using either cDNA or genomic DNA in the transgenic production of biocompetent fibrinogen in the mammary gland. In support of its position, Velander relied on the declaration and deposition testimony of its experts, Drs. David Toman, Lothar Hennighausen, and Jeffrey Rosen.

On August 16, 2001, the Board granted Garner's motion to have the allowed [**13] claims of the Velander application declared obvious. *Velander, 2001 Pat. App. LEXIS 65 at *35.* In view of the fact that Velander did not argue that his claims were separately patentable, the Board decided to analyze patentability of all of the claims based upon claim 65 of the Velander application. *2001 Pat. App. LEXIS 65 at *6.* The Board noted that claim 65 was not confined to the use of cDNA or genomic DNA and that, as far as the production of fibrinogen was concerned, the only requirement was that production yield a "recoverable" amount. Id. The Board pointed out that all of the elements of claim 65 were incontestably in the prior art and that Garner had demonstrated a motivation to produce serum proteins, including fibrinogen, in the milk of a transgenic animal. *2001 Pat. App. LEXIS 65 at *8.* At the same time, the Board accepted Velander's view of the level of one of skill in the art:

> The ordinary skilled worker would have had more than just mere 'familiarity' with transgenics. Rather, the skilled person would have had experience in expressing heterologous proteins in transgenic animals and in obtaining the expressed heterologous proteins from the body fluids of the animals, particularly from milk. The skilled [**14] worker actually should have had experience as a member of a laboratory group that produced, identified and used transgenic animals to express heterologous proteins in the body fluids of transgenic animals, particularly in the mammary glands of transgenic animals.

*2001 Pat. App. LEXIS 65 at *8-9* (quoting Velander Motion No. 41 at 3-4). The Board then moved on to Velander's main point in opposition to Garner's contention that the invention that was the subject of the '184 application was obvious. Turning to Velander's argument that a person having ordinary skill in the art would not have had a reasonable expectation of success based on the teachings in the art as of the critical date, *2001 Pat. App. LEXIS 65 at *9,* the Board noted that a reasonable expectation of success is to be assessed from the perspective of one of ordinary skill in the art at the time the invention was made. *Life Techs., Inc. v. Clontech Lab., Inc., 224 F.3d 1320, 1326 (Fed. Cir. 2000).* With that in mind, the Board proceeded to analyze the expert declarations and the cited prior art to determine whether, to one of ordinary skill in the art as of the critical date, there would have been a reasonable expectation of success [**15] in producing transgenic animals capable of expressing the protein fibrinogen in biologically active form.

Dr. Alan Colman, Garner's expert, testified by declaration that there would have been a reasonable expectation of success. The Board cautioned, however, that the Colman testimony was to be accorded little weight, except where it was supported by cited literature. *Velander, 2001 Pat. App. LEXIS 65 at *11.* Addressing the Hennighausen Review, the Board noted its discussion of the advantages of the use of transgenic milk production of proteins over production of proteins from cell culture systems and its identification of serum proteins, especially blood clotting factors, as ideal proteins for production using transgenic animals. *2001 Pat. App. LEXIS 65 at *11-12.* The Board stated that "according to the Hennighausen review, success had already been achieved for several human proteins, including serum proteins like protein C, but at widely variable and generally low expression levels (pp. 5-6) . . . ." *2001 Pat. App. LEXIS 65 at *11.* The Board added that

[*1366] the Review "created the impression that producing transgenic mammalian livestock is expensive, technically challenging, and laborious, but nevertheless a viable option for producing [**16] proteins." *2001 Pat. App. LEXIS 65 at *12*. In addition, the Board pointed out that Dr. Colman cited the Meade patent as showing a reasonable expectation of success, and it noted that "Meade provides motivation to switch from cell cultures to transgenic milk production, noting cost advantages (1:15-21) and increased reliability (1:41-45), and (vis-a-vis prokaryotes) proper post- translational modifications (1:36-41)." Id. Finally, the Board observed that "Meade identifies many proteins subject to its method, including serum proteins (3:31-40)." Id.

The Board performed a similar analysis with respect to the declarations of Velander's experts, Drs. Hennighausen, Rosen, and Toman, all of whom testified as to the lack of a reasonable expectation of success. Again, as it did with Dr. Colman, the Board cautioned against reliance upon expert testimony that was not sufficiently supported. The Board determined that Dr. Hennighausen's conclusions, like those of Dr. Colman, were "entitled to little weight beyond the corroborating references that he cites." *2001 Pat. App. LEXIS 65 at *13*. One such reference was an article by Dr. Hennighausen himself (the "1997 Hennighausen article"), n6 in which he noted some of the difficulties [**17] in expressing proteins in transgenic animals. The Board, however, concluded that the two-page Hennighausen article, published in 1997 over three years after the critical date, was not convincing support for Dr. Hennighausen's declaration because it was not specific enough as to the problems with transgenic milk production. *Velander, 2001 Pat. App. LEXIS 65 at *13*. The Board also stated that there are few circumstances in which a later publication can be used to show earlier knowledge. Id. Cf. *In re Koller, 613 F.2d 819, 824 n.5 (C.C.P.A. 1980)* (discussing the narrow circumstances in which later publications can be used to show earlier knowledge). The Board pointed out that the 1997 Hennighausen article stated that there were two problems associated with the use of transgenic animal milk protein production on a large scale, specifically: (1) variable levels of production, and (2) problems with post- translational modification. n7 *Velander, 2001 Pat. App. LEXIS 65 at *13*. The Board noted that the article stated that the first problem could be solved in mice, but not livestock, and that the second problem came into play only when a high level of protein was produced because such a level of production [**18] could overwhelm the tissue's "enzymatic machinery" for performing post-translational modifications. Id. The Board further noted that claim 65 was not limited to livestock and that claim 65 required only a "recoverable" amount of biocompetent fibrinogen, making both of these problems inapplicable. Id.

n6 Hennighausen, Transgenic Factor VIII: The Milky Way and Beyond, 15 Nature Biotech. 945 (1997).

n7 Post-translation modification refers generally to the biological processing of proteins after they have been produced from their mRNA transcripts in the cell. These modifications generally involve cleavage, subunit assembly, and/or side chain addition.

In his declaration, Dr. Hennighausen expressed the view that purification of fibrinogen could be a problem. Hennighausen Declaration P 16 ("In particular, it had been known that milk contains proteases which could destroy proteins during their purification process."). But Gordon et al. (the "Gordon article"), n8 upon which Dr.

[*1367] Hennighausen relied, [**19] stated that proteins expressed by transgenic milk production were "sufficiently stable in milk." Gordon article at 1185. The Board concluded that the potential difficulties with successfully using transgenic animal milk to produce proteins postulated by Dr. Hennighausen, as well as the potential difficulties with variable levels of protein production, were entitled to little weight in assessing likelihood of success, in view of the references cited for corroboration and the language of claim 65 ("[a] transgenic nonhuman female mammal that produces recoverable amounts of biologically active human fibrinogen . . . in its milk"). *Velander, 2001 Pat. App. LEXIS 65 at *13-14.*

n8 Gordon et al., Production of Human Tissue Plasminogen Activator in Transgenic Mouse Milk, 5 Bio/Tech. 1183 (1987).

Likewise, the Board determined that Dr. Rosen's declarations were entitled to little weight beyond the corroborating references cited. *2001 Pat. App. LEXIS 65 at *17.* The Board, however, did find Dr. Rosen's statements credible when he stated, [**20] consistent with prior-art publications, that

> in 1993, it would [have been] obvious to combine [the DNA sequences encoding the three fibrinogen chains and regulatory sequences requisite for expression in the mammary gland] to target expression to the mammary gland. The only issue would have been which promoter or regulatory sequences to use from the known promoters and regulatory sequences.

Id. The Board found that Dr. Rosen's statement that fibrinogen was "more complex than any transgenic expression previously attempted" was credible to the extent it meant that fibrinogen involved assembly of more protein subunits than other proteins that had been expressed transgenically. *2001 Pat. App. LEXIS 65 at *17-18.*

The Board considered, but then discounted, Dr. Rosen's testimony about a lack of reasonable expectation of success because he did not explain how the references that he cited, the Meade patent, the Clark application, and the Rosen patent, supported his opinion that a skilled worker would not have expected to succeed. Id.

The Board also considered Dr. Rosen's testimony that the expression of transgenes was highly variable; it discounted this testimony, however, [**21] insofar as it applied to the Velander application. *2001 Pat. App. LEXIS 65 at *18.* The Board stated that Velander's claims only require the expression of "more than minuscule trace amounts." *2001 Pat. App. LEXIS 65 at *7.* The Board stated that Dr. Rosen's testimony about the "variability" in expression level did not mean that the skilled worker would have expected no transgenic fibrinogen to be produced. *2001 Pat. App. LEXIS 65 at *18.*

Additionally, the Board considered Dr. Rosen's testimony that cell lines could not be used to predict the possible adverse effects associated with transgenic expression in the mammary glands of animals. The Board found that Yarus et al. (the "Yarus article"), n9 the only prior-art publication upon which Dr. Rosen relied, did not support Dr. Rosen's opinion. Id. First, the Board noted that the Yarus article was published after the critical date. The Board also noted that the Yarus article reported two cases in which adverse effects had been observed in connection with the transgenic expression of hormones. n10 The Board concluded that one of

[*1368] skill in the art would not have considered any of these possible problems insurmountable for transgenic fibrinogen production. Id.

n9 Yarus et al., Engineering Transgenes for Use in the Mammary Gland, 18 Genetic Eng'g 57 (1996).

[**22]

n10 The two cases of adverse effects identified in the Yarus article were (1) systemic physiological effects that resulted from secretion of the produced proteins into the blood stream of the animal and (2) direct developmental effects that occurred on mammary gland epithelial cells or their underlying support cells. Both problems are associated with secretion of enzymes that can alter the growth patterns of other cells.

Finally, the Board analyzed Dr. Toman's declaration, in which he stated that expression in transgenic animals is variable and that cell lines are not predictive of expression problems in transgenic animals. *2001 Pat. App. LEXIS 65 at *19*. The Board concluded that "Toman's conclusion that the art was unpredictable and offered little chance of success . . . must be read in light of Toman's focus on predictable expression levels and the lack of correlation with cell lines, neither of which are limitations of claim 65." *2001 Pat. App. LEXIS 65 at *19*. The Board concluded that "Toman's conclusion is less credible than the wealth of contemporaneous publications offering a contrary view." Id. Summarizing, the Board [**23] noted that

> Velander['s] witnesses consistently point to the variability of expression to indicate that the art was not predictable, but also rely on that variability to discount Garner's contention that genomic DNA yields unexpectedly good results. The cited publications collectively indicate that, at the critical date, a person having ordinary skill in the art would have expected considerable variability in yields (including no yield), even among animals subjected to the same protocol. A person having ordinary skill in the art would have viewed such variability as an indication of the expense, time, and effort involved in producing transgenic mammals and selecting those with "recoverable" yields, but not as an indication that success would be unlikely.

*2001 Pat. App. LEXIS 65 at *20.*

Based upon its analysis, the Board granted Garner's motion, concluding that Velander's claims 64-73 from the '184 application directed to transgenic mammals capable of expression of fibrinogen in their milk were unpatentable as obvious. The Board stated:

> For this motion, the preponderance of the evidence supports the findings that the level of skill in the art was high; all of the [**24] elements of the invention, including the DNA, the promoters, and the experience with transgenic animals existed in the prior art; and the art provided ample motivation for one skilled in the art to attempt to produce transgenic animals engineered to express human fibrinogen. One skilled in the art would have expected the process to be challenging, expensive, time- consuming, and tedious, but would not have expected the process to require undue experimentation. Furthermore, one skilled in the art would have been well acquainted with the inadequacy of cell cultures as a basis for predicting success in transgenic animals and thus would not have counted on such results to provide much encouragement or discouragement. Finally, absolute predictability is not a requirement for obviousness.

*2001 Pat. App. LEXIS 65 at *21.*

Velander timely moved for reconsideration of the Board's decision. In its motion, it argued that the Board had "misapprehended or overlooked" its duty to specify the prior-art references upon which it was relying in coming to its conclusion of obviousness. Velander also argued that the Board had failed to identify references that would support a motivation to combine the elements [**25] of the invention found in the prior art. Velander further argued that the Board had erred because it "did not point to any prior art publication that could be construed as evidencing the reasons for expecting success in the transgenic production of fibrinogen, as claimed."

[*1369] on motions are in fact present . . . ." *Garner v. Velander, Reconsideration Decision 2001 Pat. App. LEXIS 65 at *9.* Turning to Velander's contention that there was no "prior art publication that could be construed as evidencing reasons for expecting success in the transgenic production of fibrinogen," the Board noted that the decision on the motions contained the following findings based on the statement of material facts in Garner's preliminary motion 2 (Paper No. 22):

> m. As of the critical date, biocompetent human fibrinogen had been produced using cultured mammalian cells transfected with the cDNAs encoding the three [fibrinogen] chains (Paper No. 22 at 7, P 12 (uncontested)).
>
> n. As of the critical date, several introduced proteins had been produced in the milk of transgenic mammals. The prior [**26] art included teachings or suggestions for the production of blood and serum proteins in the milk of transgenic mammals (Paper No. 22 at 10-11, P 16).

*2001 Pat. App. LEXIS 65 at *5.* The Board noted that the references cited in Garner's Paper No. 22 in paragraph 16 of the statement of facts were the Meade patent, the Rosen patent, and the Clark application. On reconsideration, the Board again found that all of the elements of Velander's claims were present in the prior art. The critical inquiry then reduced to whether there was, from the prior art, a motivation to combine these elements and a reasonable expectation of success in producing transgenic animals capable of expressing the protein fibrinogen in biologically active form if those elements were combined. Velander noted the Board's discussion of the Hennighausen Review and the Meade patent but urged that these references related only to "motivation" to combine. *2001 Pat. App. LEXIS 65 at *9.* The Board responded that motivation to combine and reasonable expectation of success are "logically associated and thus it should not be surprising that they are discussed together." Id. The Board went on to point out that the Hennighausen Review touted the [**27] use of transgenic animals for the production of other blood serum proteins analogous to fibrinogen, although admittedly less complex, and that the Meade patent described the production of a blood protein in transgenic mammal milk. In light of this analysis, the Board found that "Velander has not justified relief from the order granting Garner preliminary motion 2, which held all of Velander's involved claims to be unpatentable." Id. Velander now appeals to us. We have jurisdiction pursuant to *28 U.S.C. § 1295(a)(4)(A).*

ANALYSIS

Velander makes essentially three arguments on appeal. First, it contends that the Board erred in its allocation of the burden of proof. Velander asserts that the Board improperly placed on it, with respect to the prior art, the burden of proving "an expectation of failure," rather than requiring Garner to prove a reasonable expectation of success to substantiate obviousness. Second, it contends that the Board erred in refusing to consider the testimony of its independent experts. According to Velander, their testimony provided substantial evidence in support of the proposition that the prior art did not give rise to a reasonable [**28] expectation of success in expressing fibrinogen in mammary gland cells in vivo. Third, Velander argues that substantial evidence does not support the Board's finding that, to one of ordinary skill in the art, the prior art provided a reasonable expectation of success in expressing fibrinogen in mammary gland cells in vivo. Accordingly, Velander urges, the Board's ultimate conclusion of obviousness is incorrect as a matter of law.

I.

Burden of Proof

As noted above, before the Board, Garner was required to establish by a

[*1370] preponderance of the evidence that the claims of the Velander application were unpatentable. The preponderance of the evidence standard requires the trier of fact "to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the [judge] of the fact's existence." *Bosies v. Benedict, 27 F.3d 539, 542 (Fed. Cir. 1994)* (quoting *In re Winship, 397 U.S. 358, 371-72, 25 L. Ed. 2d 368, 90 S. Ct. 1068 (1970)* (alterations in original) (citations omitted) (Harlan, J., concurring)). Velander argues that instead of requiring Garner to prove [**29] that the prior art showed a reasonable expectation of success, the Board improperly shifted the burden of proof by requiring Velander to establish that the prior art showed an expectation of failure. Velander asserts that the Board "clearly did not require Garner to prove that the prior art showed a reasonable expectation of successfully expressing fibrinogen in mammary cells in vivo, for nowhere does the Board state in its decision that Garner did so."

Velander's burden of proof argument is without merit. To begin with, the Board clearly understood that Garner had the burden of proof and what that burden was. In its August 16, 2001 decision, the Board stated, "Garner bears the burden of justifying the relief it seeks." *Velander, 2001 Pat. App. LEXIS 65 at *21.* Then, in the very next sentence, the Board stated that "the preponderance of the evidence" supported the pertinent findings of fact bearing on obviousness. Id.

Neither did the Board, while correctly articulating the burden of proof, nevertheless misapply it, as Velander suggests. As Garner points out, the Board specifically found that Garner had proven the following facts by a preponderance of the evidence: (1) the level of skill [**30] in the transgenic art was high; (2) all of the elements of the '184 application existed in the prior art; and (3) the prior art provided ample motivation for the skilled worker to produce transgenic animals engineered to express human fibrinogen. Id. In addition, we do not think that the Board required Velander to prove an expectation of failure, as argued by Velander. We agree with Garner that what happened was that the Board simply found unpersuasive Velander's rebuttal testimony that there was no reasonable expectation of success. See *WMS Gaming, Inc. v. Int'l Game Tech., 184 F.3d 1339, 1359 (Fed. Cir. 1999)* (Objective evidence of non-obviousness may be used by a patentee "to rebut a prima facie case of obviousness based on prior art references.").

For example, the Board considered the 1997 Hennighausen article and determined that it was of limited probative value in assessing nonobviousness, except to the extent that it showed either (i) prior art knowledge of some of the problems associated with transgenic milk protein expression or (ii) that the problems it described actually applied to the transgenic production of fibrinogen. *Velander, 2001 Pat. App. LEXIS 65 at *13.* [**31] The Board concluded that the article failed to describe any specific problem applicable to the transgenic expression of fibrinogen, and that the two problems mentioned in the article (i.e., large-scale production in livestock and problems with post- translational modifications at high expression levels) were not relevant to the claim at issue in the Velander application because the claim was not limited to livestock or a high level of production. *2001 Pat. App. LEXIS 65 at *13-14.* Based upon its analysis, the Board concluded that the article did not rebut Garner's case. The Board did not misplace the burden of proof on Velander.

Additionally, the Board did not require Velander's experts to prove an expectation of failure, as argued by Velander. Rather the Board simply looked for an objective

[*1371] basis for the opinions of the experts with respect to the asserted lack of a reasonable expectation of success. Because the Board found no objective basis for the opinions of Velander's experts, the Board gave these declarations little probative weight as rebuttal to Garner's evidence.

II.

Velander's Expert Witnesses

Velander argues that the Board erred by refusing to consider the testimony of its expert witnesses, [**32] Drs. Rosen, Hennighausen, and Toman. According to Velander, this error was prejudicial because the expert testimony that the Board disregarded provided "substantial evidence" that there was no reasonable expectation in the prior art that fibrinogen could be successfully expressed in mammary gland cells in vivo. In making this argument, Velander points, inter alia, to the Board's statement that the "broad conclusions" of Velander's experts were "entitled to little weight beyond the corroborating references" the experts cited. *2001 Pat. App. LEXIS 65 at *17.* Velander also points to the Board's statement that the "litigation-driven testimony" of one of its experts was to be accorded less weight than his "ante litem motam writings."

n11 Id. Garner responds that the Board did not improperly disregard any of the expert testimony that was offered by Velander. It asserts that the Board did exactly what a fact finder must do, consider all of the evidence before it and accord the proper and appropriate weight to the evidence.

N11 "Ante litem motam" refers to a time when a declarant had no motive to distort the truth. See *In re Hayden's Estate, 176 Misc. 1078, 29 N.Y.S.2d 852, 856 (N.Y. Sur. Ct. 1941).*

[**33]

We agree with Garner that the Board did not fail to consider the testimony of Velander's expert witnesses. As seen above, in the case of both Garner's and Velander's experts, what the Board consistently did was accord little weight to broad conclusory statements that it determined were unsupported by corroborating references. It is within the discretion of the trier of fact to give each item of evidence such weight as it feels appropriate. See *Newell Cos., Inc. v. Kenney Mfg. Co., 864 F.2d 757, 787-88 (Fed. Cir. 1988)* ("Determining the weight and credibility of the evidence is the special province of the trier of fact.

The trier of fact must not only identify the prior art, its scope and content, but it must also weigh all the evidence, impose the viewpoint of the person of ordinary skill, and determine if the burden of proof has been met.") (citation omitted). In giving more weight to prior publications than to subsequent conclusory statements by experts, the Board acted well within that discretion. See *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 294 (Fed. Cir. 1985)* ("Lack of factual support for expert opinion going to [**34] factual determinations, however, may render the testimony of little probative value in a validity determination."); *Carella v. Starlight Archery & Pro Line Co., 804 F.2d 135, 138 (Fed. Cir. 1986)* ("Although in some circumstances unsupported oral testimony can be sufficient to prove prior knowledge or use, it must be regarded with suspicion and subjected to close scrutiny.").

Dr. Rosen's Testimony

Velander asserts that the Board ignored Dr. Rosen's declaration and deposition testimony that the prior art did not show a reasonable expectation of success of transgenically expressing fibrinogen in the milk of animals. The Board, however, did consider all of Dr. Rosen's declaration and oral testimony, finding those portions of his testimony that were consistent with the scientific literature to be probative and credible. *Velander, 2001 Pat. App. LEXIS 65 at *17.* Because

[*1372] it was consistent with the scientific literature, the Board did find credible Dr. Rosen's statement that

> in 1993, it would [have been] obvious to combine [the DNA sequences encoding the three fibrinogen chains and regulatory sequences requisite for expression in the mammary gland] to target [**35] expression to the mammary gland. The only issue would have been which promoter or regulatory sequences to use from the known promoters and regulatory sequences.

Id. The Board also found that Dr. Rosen's statement that fibrinogen was "more complex than any transgenic expression previously attempted" credible to the extent it meant that "fibrinogen involved the assembly of more protein subunits than the other proteins" that had been expressed transgenically. *2001 Pat. App. LEXIS 65 at *17-18.*

The Board considered, but then discounted, Dr. Rosen's testimony about a lack of reasonable expectation of success because he did not explain how the references that he cited, the Meade patent, the Clark application, and the Rosen patent, supported his opinion that a skilled worker would not have expected to succeed.

The Board also considered Dr. Rosen's testimony that the expression of transgenes was highly variable but discounted this testimony as it applied to Velander's claims. *2001 Pat. App. LEXIS 65 at *18.* Velander's claims only require the expression of "more than minuscule trace amounts." *2001 Pat. App. LEXIS 65 at *7.* The Board stated that Dr. Rosen's testimony about the "variability" in expression level did not mean [**36] that a skilled worker would have expected no transgenic fibrinogen to be produced. *2001 Pat. App. LEXIS 65 at *18.*

Finally, the Board considered Dr. Rosen's testimony that cell lines could not be used to predict the possible adverse effects associated with transgenic expression in the mammary glands of animals. The Board found that the Yarus article, the only document relied on by Dr. Rosen, did not support his opinion. Id. The Board noted that the Yarus article reported two cases in which adverse effects had been observed, each relating to the transgenic expression of hormones. Because fibrinogen is not a hormone and has no potent biological activity, n12 the Board concluded that one of skill in the art would not have considered any of these possible problems insurmountable for transgenic fibrinogen production. Id.

> n12 Fibrinogen becomes active only after specific cleavage resulting in polymerization to form a clot; it cannot alter the growth patterns of other cells as hormones can. Anthony David Smith, Oxford Dictionary of Biochemistry and Molecular Biology 231 (2000).

[**37]

Dr. Hennighausen's Testimony

Velander also asserts that the Board disregarded Dr. Hennighausen's testimony in deciding that there was a reasonable expectation of success in expressing fibrinogen in transgenic animals as of the critical date. The Board did consider Dr. Hennighausen's testimony, however, accepting it to the extent that it was corroborated by the scientific literature. The Board considered Dr. Hennighausen's testimony that protein recovery could be difficult for some proteins, but found that he did not explain why the skilled worker would have expected the recovery of fibrinogen to be problematic. In addition, the Board noted that Dr. Hennighausen's own review article as well as Houdebine n13 suggested that any possible problem in protein recovery would be readily solvable. *2001 Pat. App. LEXIS 65 at *14.*

> n13 Houdebine, Minireview: Production of Pharmaceutical Proteins from Transgenic Animals, 34 J. Biotech. 269 (1994).

[*1373] Additionally, the Board considered Dr. Hennighausen's testimony that transgenes [**38] could cause deleterious effects on the transgenic animal or its offspring. *2001 Pat. App. LEXIS 65 at *15.* The Board, however, discounted this testimony because it was not supported by the documents to which Dr. Hennighausen pointed: Burdon et al., n14 Wall et al., n15 and Shamay et al. n16 Each of these references taught that the expression of a specific milk protein, whey acidic protein ("WAP"), could lead to impairment or loss of lactation. The Board found Dr. Hennighausen's testimony regarding the deleterious effects of transgenes unpersuasive because none of the cited references taught that "the technology was unworkable" and because Dr. Hennighausen failed to provide "any basis for generalizing [the WAP] problem to other proteins." *2001 Pat. App. LEXIS 65 at *14-15.*

n14 Burdon et al., Expression of Whey Acidic Protein Transgene During Mammary Development, 266 J. Biol. Chem. 6909 (1991).

n15 Wall et al., High-level Synthesis of a Heterologous Milk Protein in the Mammary Glands of Transgenic Swine, 88 P.N.A.S. 1696 (1991).

n16 Shamay et al., Expression of the Whey Acidic Protein in Transgenic Pigs Impairs Mammary Development, 1 Transgenic Res. 124 (1992).

[**39]

The Board also considered Dr. Hennighausen's testimony that cell cultures do not necessarily correlate with transgenic animal results. *2001 Pat. App. LEXIS 65 at *15-16.* Again, however, the Board discounted the testimony because it determined that the references cited by Dr. Hennighausen, Furth et al. n17 and Whitelaw et al., n18 did not support his opinion. Those references taught that expression enhancers do not necessarily operate in the same way in cell culture and transgenic animals. In his deposition, however, Dr. Hennighausen acknowledged that in vitro cell culture data are at least predictive of protein expression, if not activity and secretion.

n17 Furth et al., The Variability in Activity of the Universally Expressed Human Cytomegalovirus Immediate Early Gene 1 Enhancer/Promoter in Transgenic Mice, 19 Nucleic Acids Res. 6205 (1991).

n18 Whitelaw et al., Targeting Expression to the Mammary Gland: Intronic Sequences Can Enhance the Efficiency of Gene Expression in Transgenic Mice, 1 Transgenic Res. 3 (1991).

[**40]

Finally, the Board considered Dr. Hennighausen's testimony that purification of a protein transgenically produced in milk may be problematic due to the presence of proteases in milk. *2001 Pat. App. LEXIS 65 at *16.* The Board gave this testimony little weight because the Gordon article, see footnote 8 above, the reference to which Dr. Hennighausen pointed, did not support his declaration. *2001 Pat. App. LEXIS 65 at *16.* The Gordon article taught that tissue plasminogen activator ("tPA") was successfully expressed and "sufficiently stable in milk." Similarly, according to the Hennighausen Review, various other blood proteins, including blood coagulation factor IX, a1- antitrypsin, and protein C, had been successfully produced transgenically in milk. Finally, Clark et al. n19 had reported that several blood proteins of biomedical importance, such as a1-antitrypsin, tPA, and antithrombin III, existed naturally in milk. We cannot say the Board abused its discretion in giving more weight to the scientific literature than to Dr. Hennighausen's testimony.

n19 Clark et al., Pharmaceuticals from Transgenic Livestock, 5 TIBTECH 20 (1987).

[**41]

Dr. Toman's Testimony

Finally, Velander contends that the Board incorrectly criticized Dr. Toman's declaration and ignored Dr. Toman's deposition testimony. As in the case of Drs. Rosen and Hennighausen, however, the Board did consider Dr. Toman's testimony. It concluded that the testimony was "starkly at odds in tone with the contemporaneous literature" and "less credible

[*1374] than the wealth of contemporaneous publications . . . ." *2001 Pat. App. LEXIS 65 at *19.* The Board noted that although Dr. Toman indicated that one of skill in the art would not have had an expectation of success due to the relative complexity of fibrinogen, he did not point to anything in the scientific literature supporting that view.

As can be seen from the discussion of the Board's consideration of the testimony of Velander's experts, Velander's complaint really is with the way in which the Board, as the trier of fact, weighed and assessed the evidence. That complaint goes to the sufficiency of the evidence. It is to that issue that we now turn.

III.

Sufficiency of the Evidence

On appeal, we review the Board's ultimate conclusion of obviousness without deference, while we review the Board's underlying factual determinations [**42] for substantial evidence. *In re Gartside, 203 F.3d 1305, 1316 (Fed. Cir. 2000).* Substantial evidence "means such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *Consol. Edison Co. v. NLRB, 305 U.S. 197, 229, 83 L. Ed. 126, 59 S. Ct. 206 (1938).* Our review of the Board's factual findings for substantial evidence examines the record as a whole, taking into account evidence that supports as well as detracts from those findings. *Gartside, 203 F.3d at 1312.* "The possibility of drawing two inconsistent conclusions from the evidence," however, will not render the Board's findings unsupported by substantial evidence. *Consolo v. Fed. Mar. Comm'n, 383 U.S. 607, 620, 16 L. Ed. 2d 131, 86 S. Ct. 1018 (1966).* In other words, if the evidence of record will support several reasonable but contradictory conclusions, we will not find the Board's decision unsupported by substantial evidence because the Board chose one finding over another plausible alternative. *In re Jolley, 308 F.3d 1317, 1320 (Fed. Cir. 2002).* Here, the Board determined that the preponderance of the evidence [**43] supported the conclusion that claims 64-73 of the '184 application were obvious as of the critical date based on the following findings: (1) all the elements of Velander's claim 65, and by extension all of Velander's involved claims and all of Garner's claims, were in the prior art; (2) there was a motivation in the prior art to combine those elements; and (3) one of ordinary skill in the art would have had a reasonable expectation of success in generating a recoverable amount of biologically active fibrinogen.

Velander's main argument on appeal is that the decision of the Board is not supported by substantial evidence. Velander does not dispute that all of the elements of claim 65 were in the prior art and that there was a motivation to combine those elements. Velander argues, however, that as of February 18, 1993, one of ordinary skill in the art would not have had a reasonable expectation of success in producing a recoverable amount of biologically active fibrinogen from a "transgenic non-human female mammal that produces recoverable amounts of biologically active human fibrinogen . . . in its milk," as required by claim 65 of the '184 application. Velander argues that the Hennighausen [**44] Review and the Meade patent only showed a motivation to combine and not a reasonable expectation of success, and that the Rosen patent, the Clark application, and the Greenberg article did not establish a reasonable expectation of success.

Velander argues that the Hennighausen Review does not demonstrate a reasonable likelihood of success for several reasons: (1) because fibrinogen is not listed in the Review in the "table of foreign proteins that had been expressed in the milk of transgenic animals before 1990"; (2) because

[*1375] "none of the proteins listed in [the table] is comparable to fibrinogen in size or complexity"; and (3) because the article teaches that there are "numerous problems, complications and uncertainties in producing foreign proteins in transgenic animals." Essentially, as it did before the Board, Velander urges that fibrinogen is more complex than other proteins successfully expressed in transgenic systems and that, as of the critical date, there were various problems in connection with the transgenic expression of proteins in milk.

As far as the Meade patent is concerned, Velander argues that the patent only provides a general disclosure for producing foreign [**45] proteins in the milk of transgenic animals and that its only example is tPA, which Velander argues would give no reasonable expectation of success because tPA is five times smaller than fibrinogen. Velander concedes that Meade suggests the use of the transgenic technique for a number of proteins, including serum proteins, but points out that fibrinogen is not specifically mentioned. Velander also argues that Meade cannot teach an expectation of success in combination with the Hennighausen Review, as stated in the Board's reconsideration decision, because the original decision on the motions acknowledged that cell culture expression of fibrinogen was not predictive of the success of the expression in transgenic animals. *Velander, 2001 Pat. App. LEXIS 65 at *16, 20, 21.*

Velander contends that the remaining references relied on by Garner also do not provide substantial evidence to support the Board's decision. In arguing that the Rosen patent, which teaches expressing proteins in a transgenic animal generally, does not provide substantial evidence for the Board's finding of a reasonable likelihood of success, Velander argues that the patent "nowhere states or suggests that multi-chain proteins such [**46] as fibrinogen could be successfully expressed." Velander also argues that Dr. Rosen's statement that he "had no idea of making fibrinogen or any other protein like it in this patent" shows that this reference does not provide evidence for the Board's conclusion. Velander contends that the Clark application, like both the Meade and Rosen patents, teaches expressing proteins in a transgenic animal generally, that the only examples in the application are directed to preparing DNA constructs encoding Factor IX and a1-antitrypsin, as well as fusion proteins containing the -lactoglobulin gene, and that nowhere in the reference is there the suggestion that fibrinogen could be successfully expressed. Finally, Velander asserts that the Greenberg article, co-authored by Dr. Rosen, provides support, along with Dr. Rosen's deposition testimony and declaration, for why Dr. Rosen, in light of his experience with FSH (a multimeric protein expressed transgenically), believed that the transgenic expression of FSH in milk was not predictive of a successful outcome for transgenically expressing fibrinogen.

Garner responds that the decision of the Board is supported by substantial evidence. It states [**47] that, prior to the critical date, the prior art suggested that transgenic animals would be useful in producing plasma proteins in their milk. Garner cites to the Meade patent, the Rosen patent, the Clark application, and the Greenberg article as demonstrating that, as of the critical date, a number of heterologous proteins had been expressed in transgenic animals using generally accepted transgenic techniques and that successful transgenic production of proteins was normal in the art. Garner also points to human proteins with varying structures being produced in the milk of transgenic animals prior to the critical date. These proteins included blood coagulation Factor IX, a1-antitrypsin, interleukin 2, tPA, growth hormone, protein C, cystic fibrosis transmembrane

[*1376] conductance regulator protein, serum albumin, CD4, Y-interferon, urokinase, and FSH. n20

n20 See the Hennighausen Review, supra, for Factor IX, a1-antitrypsin, interleukin 2, tPA, growth hormone, protein C, and urokinase; DiTullio et al., Production of Cystic Fibrosis Transmembrane Conductance Regulator in the Milk of Transgenic Mice, 10 Biotech. 74 (1992), for cystic fibrosis transmembrane conductance regulator protein; Shani et al., Expression of Human Serum Albumin in the Milk of Transgenic Mice, 1 Transgenic Res. 195 (1992), for serum albumin; Yu et al., Functional Human CD4 Protein Produced in Milk of Transgenic Mice, 6 Mol. Biol. Med. 255 (1989), for CD4; Drobrovolsky et al., Human -Interferon Expression in the Mammary Gland of Transgenic Mice, 319 FEBS Letters 181 (1993), for -interferon; and the Greenberg article, supra, for FSH.

[**48]

Garner's principal point is that one of skill in the art would have expected success because fibrinogen shares a number of important characteristics with many of the previously produced proteins that had been expressed in the milk of transgenic animals as of the critical date. Thus, Garner notes (1) that fibrinogen is a blood protein, similar in that respect to Factor IX, a1- antitrypsin, tPA, protein C, serum albumin, and urokinase; (2) that fibrinogen is a multimer requiring post-translational modifications, including multimer assembly, in order for it to be active, similar to FSH and Protein C; and (3) that fibrinogen requires assembly from several different monomers, which are encoded by several different DNA sequences, to form its biologically active multimeric complex, similar to FSH. All of these proteins had been successfully expressed in the milk of transgenic animals prior to the critical date. Garner urges that there was no reason for one of ordinary skill in the art to expect anything other than success in the production of at least some (i.e., a recoverable amount) of transgenic fibrinogen in mammary gland cells in vivo.

In order to affirm the Board's decision, [**49] we must be convinced that substantial evidence supports the Board's conclusion that Garner established by a preponderance of the evidence that the claims of the Velander application were unpatentable. As noted, Velander does not dispute that all of the elements of claim 65 of the '184 application were in the prior art. Neither does it dispute that there was a motivation to combine those elements. Thus, as seen, the case boils down to the question of whether, as of the critical date, one of ordinary skill in the art would have had a reasonable expectation of success in producing a recoverable amount of biologically active fibrinogen from a "transgenic non-human female mammal that produces recoverable amounts of biologically active human fibrinogen . . . in its milk," as required by claim 65. What that means for us is that we must decide whether there is (i) relevant evidence that a reasonable mind might accept as adequate to support a conclusion (substantial evidence) that (ii) supports the Board's conclusion that Garner established that it was more probable than not (a preponderance of the evidence) that, as of the critical date, one of ordinary skill in the art would have had a reasonable [**50] expectation of success in generating a recoverable amount of biologically active human fibrinogen. This is a close case. However, at the end of the day, we cannot say that Velander has established that the Board's decision is not supported by substantial evidence.

We have set forth in considerable detail the evidence that was before the Board and the contentions of the parties with respect to that evidence. As discussed, it is Velander's position that the complexity of fibrinogen and the difficulties and uncertainties that would necessarily be associated with the production of human fibrinogen in a transgenic system bar the

[*1377] conclusion that, as of the critical date, there was the required reasonable expectation of success. However, the Board came to grips with this point when it stated:

> The cited publications collectively indicate that, at the critical date, a person having ordinary skill in the art would have expected considerable variability in yields (including no yield), even among animals subjected to the same protocol. [That person] would have viewed such variability as an indication of the expense, time, and effort involved in producing transgenic mammals and selecting [**51] those with "recoverable" yields, but not as an indication that success would be unlikely.

*2001 Pat. App. LEXIS 65 at *20.*

As argued by Garner and mentioned above, fibrinogen shares a number of important characteristics with many of the previously produced proteins that had been expressed in the milk of transgenic animals: (1) fibrinogen is a blood protein, similar, in that respect, to Factor IX, a1-antitrypsin, tPA, protein C, serum albumin, and urokinase; n21 (2) fibrinogen is a multimer requiring post-translational modifications including multimer assembly in order for it to be active, similar to FSH and Protein C; n22 and (3) fibrinogen requires assembly from several different monomers, which are encoded by several different DNA sequences, to form its biologically active multimeric complex, similar to FSH. n23 Garner's references present substantial evidence supporting the Board's finding that one of ordinary skill in the art would have had a reasonable expectation of success in the production of at least some (i.e., a recoverable amount) of transgenic fibrinogen in mammary gland cells in vivo. That is because, as of the critical date, proteins with similar characteristics had successfully [**52] been produced in transgenic milk systems.

n21 See the Hennighausen Review, supra, for Factor IX, a1-antitrypsin, tPA, protein C, and urokinase; Shani et al., supra, for serum albumin; and the Greenberg article, supra, for FSH.

n22 See the Hennighausen Review, supra, for protein C and the Greenberg article, supra, for FSH.

n23 See the Greenberg article, supra, for FSH.

As noted, Velander argues that the Hennighausen Review and the Meade patent cannot be used to show a reasonable likelihood of success because fibrinogen is not specifically listed in either of those publications and because of the significant problems, complications, and uncertainties described in these publications for transgenic milk protein production. The Board recognized the problems associated with transgenic milk protein production, finding that "the review creates the impression that producing transgenic mammalian livestock is expensive, technically challenging, and laborious, but nevertheless [**53] a viable option for producing proteins." *2001 Pat. App. LEXIS 65 at *12.* Velander also argues that the 1997 Hennighausen article showed that one of skill in the art would not have had a reasonable expectation of success. The Board addressed this argument, stating:

> Obviousness, and expectation of success, are evaluated from the perspective of a person having ordinary skill in the art at the time of the invention. While later publications may explain what was known earlier, it would be wrong to impute later-recognized insights--or possible obstacles--to the knowledge available to those skilled in the art at the time of the invention. . . . One skilled in the art could not be daunted by unknown obstacles although the subsequent publications might be relevant to show that the obstacles actually applied

[*1378] to the specific problems facing the inventor.

*2001 Pat. App. LEXIS 65 at *13.*

The Board pointed out the Hennighausen Review's discussion of the advantages of transgenic milk production for proteins over production using cell culture systems, identifying serum proteins, especially blood clotting factors, as ideal proteins for development. *2001 Pat. App. LEXIS 65 at *11-12.* The Board stated that, according to the [**54] Review, "success had already been achieved for several human proteins, including serum proteins like protein C, but at widely variable and generally low expression levels (pp. 5-6)." *2001 Pat. App. LEXIS 65 at *11.* The Board stated that "the review creates the impression that producing transgenic mammalian livestock is expensive, technically challenging, and laborious, but nevertheless a viable option for producing proteins." *2001 Pat. App. LEXIS 65 at *12.* While the Board recognized the problems outlined in the Hennighausen Review in connection with transgenic expression systems, especially transgenic expression of complex proteins like fibrinogen, it also recognized that claim 65 of the Velander application only required "'recoverable amounts' [which] in context means more than minuscule trace amounts." *2001 Pat. App. LEXIS 65 at *7.*

The Board also noted that Dr. Colman cited the Meade patent as showing a reasonable expectation of success and that "Meade provides motivation to switch from cell cultures to transgenic milk production, noting cost advantages (1:15-21) and increased reliability (1:41-45), and (vis-a-vis prokaryotes) proper post-translational modifications (1:36-41)." *2001 Pat. App. LEXIS 65 at *12.* The Board pointed out that "Meade [**55] identifies many proteins subject to its method, including serum proteins (3:31-40)." Id. In view of the fact that claim 65 is limited to only a recoverable amount of biologically active fibrinogen, the Board held that one of ordinary skill in the art would have had a reasonable expectation of success of producing a recoverable amount of fibrinogen, given the success with other proteins in transgenic systems, the presence of all the elements of the invention in the prior art, and the motivation to combine conceded by Velander.

Velander also argues that the remaining references relied on by Garner (i.e., the Rosen patent, the Clark application, and the Greenberg article) do not provide substantial evidence to support the Board's finding that one of skill in the art would have had a reasonable likelihood of success principally because these references do not mention fibrinogen or a protein as complex as fibrinogen. It is true that the Rosen patent, the Clark application, and the Greenberg article do not mention fibrinogen. However, it also is true that the Rosen patent, the Clark application, and the Greenberg article do demonstrate that, as of the critical date, a number of [**56] heterologous proteins had already been expressed in transgenic animals using generally accepted transgenic techniques, and that successful transgenic production of proteins was normal in the art.

Understandably, Velander directs our attention to the evidence in the record that discusses the difficulties in transgenic expression of complex proteins like fibrinogen. Such material arguably supports a conclusion contrary to the one reached by the Board. At the same time, other evidence in the record supports the conclusion reached by the Board. If the evidence will support several reasonable but contradictory conclusions, we will not find the Board's decision unsupported by substantial evidence simply because the Board chose one conclusion over another plausible alternative. *Jolley, 308 F.3d at 1320.* That is the case here. In other words, in this complex case, it is not for us to second-guess the Board's assessment of the evidence. Our task is to determine whether

[*1379] substantial evidence supports the conclusion chosen by the Board. We hold that substantial evidence supports the Board's conclusion that Garner established by a preponderance of the evidence that, as of February 18, 1993, one [**57] of ordinary skill in the art would have believed that there was a reasonable expectation of producing a recoverable amount of biologically active fibrinogen by successfully generating a "transgenic non-human female mammal that produces recoverable amounts of biologically active human fibrinogen . . . in its milk."

CONCLUSION

For, the foregoing reasons, the decision of the Board granting the preliminary motion of Garner to have the claims of the Velander application declared unpatentable as obvious is affirmed.

AFFIRMED

DISSENTBY: GAJARSA

DISSENT: GAJARSA, Circuit Judge, dissenting.

Although the majority opinion traces through a very unclear Board decision and tries with a substantial degree of specificity to supply a reasoned basis for the Board's decision, I respectfully dissent from the majority opinion because there is no reasoned basis for the Board's decision and there is no substantial evidence to support the PTO's finding of obviousness. *SEC v. Chenery Corp., 332 U.S. 194, 195, 91 L. Ed. 1995, 67 S. Ct. 1575 (1947)*; *Colorado Interstate Gas Co. v. FPC, 324 U.S. 581, 595, 89 L. Ed. 1206, 65 S. Ct. 829 (1945)*. But see In *Re Huston, 308 F.3d 1267 (Fed. Cir. 2002)*. [**58]

The Board held claims 64-73 of the Velander '184 application unpatentable for obviousness. Velander argues on appeal that there is no substantial evidence to support the Board's finding that one of ordinary skill in the art had a reasonable expectation of success regarding the production of fibrinogen in the milk of a transgenic mammal. Whether an invention is obvious is ultimately a legal conclusion. We must determine if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." *35 U.S.C. § 103*. The factual inquiries underlying obviousness include (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, (3) the level of ordinary skill in the art at the time the invention was made, and (4) any objective evidence of nonobviousness. *Graham v. John Deere Co., 383 U.S. 1, 17-18, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966)*. "The consistent criterion for determination of obviousness is whether [**59] the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *In re Dow Chem. Co., 837 F.2d 469, 473 (Fed. Cir. 1988)*. Obviousness requires one of ordinary skill in the art have a reasonable expectation of success as to the invention--"obvious to try" and "absolute predictability" are incorrect standards. *In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988)*. The presence of a reasonable expectation of success is measured from the perspective of a person of ordinary skill in the art at the time the invention was made. *Life Techs., Inc. v. Clontech Lab., Inc., 224 F.3d 1320, 1326 (Fed. Cir. 2000)*. To this end, the ultimate success of the invention is irrelevant. *Id.*

The Board's decision should pave the way to meaningful appellate review. In its decision, the Board is obligated not only to make the requisite findings based on the evidence of record, but also to explain the reasoning underlying its findings. *In re*

[*1380] *Lee, 277 F.3d 1338, 1344-45 (Fed. Cir. 2002)*. Our review of the [**60] Board's decision for substantial evidence should be restricted to the grounds relied on by the Board. See id. ("Review of an administrative decision must be made on the grounds relied on by the agency. 'If those grounds are inadequate or improper, the court is powerless to affirm the administrative action by substituting what it considers to be a more adequate or proper basis.'" (quoting *Chenery, 332 U.S. at 196*)); see also *In re Zurko, 258 F.3d 1379, 1385 (Fed. Cir. 2001)* (rejecting the PTO's argument for this court to consider additional references not relied on by the Board in reaching its conclusion of obviousness because the references did not support the Board's conclusion and, moreover, "would constitute a new ground for rejection, not considered or relied upon by the Examiner or the Board").

Here, the Board explicitly supported its finding of reasonable expectation of success on the Hennighausen review and Meade patent. In particular, the Board found persuasive the fact that both references discussed the production of blood proteins via transgenic animals:

> The Hennighausen review in particular touts the use of transgenic animals [**61] for the very class of pharmaceutical proteins (blood serum proteins) to which fibrinogen belongs. Similarly, Meade obtained a patent for production of a blood protein in transgenic mammal milk. The problems identified in the art are not presented as insurmountable or unique to blood proteins.

The Board thus found that one of ordinary skill in the art n1 would have believed, on the critical date, n2 that there was a reasonable chance of producing fibrinogen in view of the fact that the expression of other blood proteins in transgenic animals was disclosed in the Hennighausen review and Meade patent.

n1 The Board adopted Velander's definition of one of ordinary skill in the art as of the critical date as having been "knowledgeable and experienced in the expression of heterologous proteins in the milk of transgenic animals," and not just having mere familiarity with transgenics.

n2 The critical date for determining patentability under *35 U.S.C. § § 102(b) and 103* is February 18, 1993, one year before the filing date of the '068 application.

[**62]

This finding, however, was unsupported by substantial evidence because it was based on the Board's unsupported assumption, or alternatively, unsupported finding, as to the second Graham factor: the difference between the prior art and the claims at issue, as viewed from the vantage point of one of ordinary skill in the art. The Board's decision reveals its implicit assumption that one of ordinary skill in the art would have perceived the difference between the disclosed blood proteins and fibrinogen to be insignificant. Even assuming that this implicit assumption constituted an actual "finding" by the Board, it was unsupported by any evidence, let alone substantial evidence, that one of ordinary skill in the art would have agreed that the mere disclosure of blood proteins in the prior art would have led one of ordinary skill in the art to believe that fibrinogen could be expressed in transgenic non-human mammals. As we explained in Zurko:

> As an administrative tribunal, the Board clearly has expertise in the subject matter over which it exercises jurisdiction. . . . With respect to core factual findings in a determination of patentability, however, the Board cannot [**63] simply reach conclusions based on its own understanding or experience--or on its assessment of what would be basic knowledge or common sense. Rather, the Board must point to some concrete evidence

[*1381] in the record in support of those findings. To hold otherwise would render the process of appellate review for substantial evidence on the record a meaningless exercise.

Zurko, 258 F.3d at 1385-86 (citing *Baltimore & Ohio R.R. Co. v. Aberdeen & Rockfish R.R. Co., 393 U.S. 87, 91-92, 21 L. Ed. 2d 219, 89 S. Ct. 280 (1968)).*

While we cannot step into the shoes of one of ordinary skill in the art, I believe that the Board's functional definition, accepted by the majority, of fibrinogen as a blood protein was misguided. The Board implies that the mere disclosure of the production of blood proteins, in general, via transgenic animals renders obvious the expression of any other blood protein in the same way, even where the target blood protein is so much more structurally complex that one of ordinary skill in the art would be hard-pressed to determine how to produce it via transgenic means. For example, the blood protein that could be encoded from [**64] multiple genes is large and requires post-translational processing that is not controlled by any human mammary genes. Potential problems faced by one of ordinary skill might include co-integration of the three genes encoding the fibrinogen protein into the foreign genome, proper assembly and bonding of the six chains of the protein once expressed, and proper secretion of the protein from the mammary gland into the milk of the lactating animal. n3 The Board's classificatory framework of fibrinogen as blood protein seems irrelevant to resolving such potential issues.

n3 Velander raises exactly these sorts of issues on appeal, arguing that one of ordinary skill in the art would have perceived the expression of fibrinogen in transgenic animals as a formidable task due to the structural complexity of fibrinogen. For example, Velander notes that fibrinogen is not only (1) much larger than the disclosed proteins in the prior art produced in the milk of transgenic animals, but (2) derived from three genes, as opposed to one or two. Velander claims that the fact that three separate genes are necessary to produce the alpha, beta and gamma chains of the fibrinogen protein creates unique considerations as to the transgenic production of fibrinogen. In this last regard, Velander's experts testified that the assembly of the six chains of fibrinogen was uncertain due to additional difficulties of co-integrating the genes and assembling the final protein. The Board did not acknowledge these relevant arguments in its decision.

[**65]

The Board failed to determine (1) the difference, if any, between the prior art and the claims at issue as perceived by one of ordinary skill in the art, and (2) whether that difference, if any, is so significant that one of ordinary skill in the art would not entertain a reasonable expectation of success of expressing fibrinogen in transgenic non-human mammals.

For these reasons, I respectfully dissent.

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